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10/718,107	11/20/2003	Michael P. Girouard	P03155US (98554.1P3)	8886

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EXAMINER	
CHUI, MEI PING	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/718,107	GIROUARD, MICHAEL P.	
	Examiner	Art Unit	
	Helen Mei-Ping Chui	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *55,85,91,117,119 and 124* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *55,85,91,117,119 and 124* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/ are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/28/2004, 06/23/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Action

Receipt of Amendments/Remarks filed on 09/17/2007. Claims 55, 85, 91, 117, 119 and 124 are presented for examination on the merits for patentability and claims 1-54, 56-84, 86-90, 92-116, 118, 120-123 and 125-137 are cancelled. The new claim rejections and claim withdrawns are based on the claims presented in the amendment filed on 09/17/2007. Upon further search and consideration, the examiner has new ground of rejections. Accordingly, this action is non-final.

Withdrawn rejections/objections

(1) **The rejection over claims 55, 85, 91, 119 and 124** under nonstatutory obviousness-type double patenting are withdrawn because in light of the terminal disclaimer filed on 09/17/2007.

The terminal disclaimer filed on 09/17/2007 disclaiming the terminal portion of any patent granted on this application, which would extend beyond the expiration date of prior U. S. Patent No. 6,821,961 has been reviewed and is accepted. The terminal disclaimer has been recorded.

(2) **The rejection over claims 55, 85, 91, 117, 119 and 124** under 35 U.S.C. § 112 first paragraph (Scope of Enablement of the Invention) are withdrawn because in light of the amendment filed on 09/17/2007.

(3) **The rejection over claims 55, 85, 91 and 119** under 35 U.S.C. § 102(b) are withdrawn because in light of the amendment filed on 09/17/2007.

(4) **The rejection over claims 55, 85, 91, 117, 119 and 124** under 35 U.S.C. § 103(a) are withdrawn because in light of the amendment filed on 09/17/2007.

Claim Rejections - 35 USC § 112 second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection over claims 55, 85, 91, 117, 119 and 124 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, are maintained.

Response to the Arguments

Applicant argues that the language "substantially pure" is sufficiently definite to one skilled in the art. Applicant also refers the references in the examples to 80 % purity (see page 12, lines 23-26), 98 % (see page 6, lines 30-32), and 2-hydroxyestrone (see page 49, lines 21-23).

Applicant's arguments filed on 09/17/2007 have been fully considered but they are not persuasive. Applicant argues that the purity of the recited fatty acid monoester of 2-hydroxyestrogen, especially 2-hydroxyestrone or 2-hydroxyestradiol, and a fatty acid is disclosed and can be found in page 12, lines 23-26 of the instant specification; however, the disclosed compounds, which are 81 % and 80 % pure, in page 12, lines 23-26 are referred to estrone oleate and estrone eicosenoate, respectively. Since these two compounds do not contain hydroxyl functionality at the C2 position; therefore, their purity cannot represent the purity of the fatty acid monoester of an estrogen and a fatty acid, as claimed.

Similarly, applicant directs the purity of the recited fatty acid monoester compound to page 6, lines 30-32. However, the disclosed compound, which is 98 % pure, is referred to 2-bromoestrone ester of cis-11-eicosenoate, and it also do not contain hydroxyl functionality at the C2 position; therefore, its purity cannot represent the purity of the compound in the claims.

Furthermore, as acknowledged by applicant of page 49, lines 21-23, where applicant clearly admits that 2-hydroxyestrone eicosenoate is unstable due to the presence of an impurity (see page 49, line 21).

Although applicant speculates that a stable 2-hydroxyestrone eicosenoate may be produced if using pure starting material. However, it is known to one skilled in the

relevant art that the chemical reactivity of the two hydroxyl groups, 2-hydroxyl and 3-hydroxyl in 2-hydroxyestrone, is relatively similar. In fact, Nakagawa suggested that the C-2 hydroxyl group of 2-hydroxyestrogen is slightly more basic than the C-3 hydroxyl group and hence, the in vitro *O*-methylation gives the 2-methyl ether in three times larges amount than the 3-methyl ether (See Nakagawa et al. J. Pharm. Dyn. 1979, 2, 365-373). Thus, a reaction simply combining the activated fatty acid acyl chloride and 2-hydroxyestrone, as described in the specification, will not render a substantially pure 2-hydroxyestrone monoester, but a mixtures of 2-*O*, 3-*O* and 2,3-*O*-conjugated products. Fishman et al. has been demonstrated that, in vivo, the selectivity of these two indistinguishable phenolic hydroxyl groups appear to be specific due to the enzymatic participation (J.A.C.S. 1967, 89, 7147-7148; J.O.C. 1968, 33, 662-664; Biochemistry, 1969, 8, 1669-1672); however, in vitro, this is considerably more challenging for one skilled in the relevant art to achieve such regio-selectivity without any protecting strategy for the preparation of 2-hydroxyestrone eicosenoate in the claimed invention. In fact, applicant explicitly pointed out that the 2-hydroxyestrone eicosenoate is tested to be unstable and found not suitable to be use in the instant invention presumably due to the presence of undesired products and impurity in the product (See Specification, Example 12, Page 49, line 21-23). In addition, Seeger et al. also observed that 2-hydroxyestrone is rapidly oxidized in air in their experiments; thus special handling and procedures are required when utilizing 2-hydroxyestrone in their experiments (Life Science, 1997, 61, 865-868). Therefore, a substantially pure fatty acid monoester claimed in the instant invention cannot be supported without further evidences.

New Ground of Claim Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 55, 85, 91, 117, 119 and 124 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 55, 91, 117, 119 and 124 introduce new matter as the claims recite the limitation "the fatty acid consists of at least 20 carbon atoms". Similarly, claim 85 introduce new matter as the claim recites the limitation "the fatty acid consists of more than 19 carbon atoms". There is no support in the specification for the fatty acid consists of 21, 23, 25 or higher number of carbon atoms. The limitation of "the fatty acid consists of at least 20 carbon atoms" was not described in the specification as filed, and person skilled in the art would not recognize in the applicant's disclosure a description of the invention as presently claimed. The specification discloses the fatty acid consists of 18 (oleic), 20 (eicosenoic), 22 (docosenoic) and 24 (tetracosenoic) carbon atoms" (see page 8, lines 7-8 and Examples

1-12), but does not describe the fatty acid consists of 21, 23, 25 or higher number of carbon atoms. There is no guidance in the specification to select the fatty acid carbon atom more than 24. Therefore, it is the Examiner's position that the disclosure does not reasonably convey that the inventor had possession of the subject matter of the amendment at the time of filing of the instant application.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 55, 85, 91, 117, 119 and 124 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(1) Claims 55, 85, 91, 117, 119 and 124 recite the term "derivative". The term "derivative" is defined, according to Merriam-Webster's Collegiate Dictionary (tenth Edition), as a chemical substance related structurally to another substance and theoretically derivable from it, or a substance that can be made from another substance (see page 311, derivative (n): meaning 4 and 5). However, the term "derivative" is not defined by the claim, and the specification does not provide a standard for ascertaining the requisite degree; it is unclear that the term "derivative" means a structural derivative or a functional derivative in relation to the recited estrogens, 2-hydroxyestrone or 2-hydroxyestradiol. Therefore, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention, and thus rendering the claim indefinite.

(2) Claims 55 and 85 recite the term "precursor", however, this term is not defined by the claim, and the specification does not provide a standard for ascertaining the requisite degree. It is unclear that the term "precursor" means the pro-drug, the starting material, the structural or the functional precursor in relation to the recited fatty acid monoester. Therefore, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention, and thus rendering the claim indefinite.

(3) Claim 85, 117 and 119 recite that "the method comprising administering to said mammal .....a substantially pure fatty acid monoester, or a precursor thereof, of an estrogen and a fatty acid". It is unclear that "the fatty acid monoester of an estrogen and a fatty acid" recite in the claims refer to a single molecule formed from the recited estrogen and a fatty acid, or refer to 2 separate molecules, which is formed from the recited estrogen mixed with a fatty acid. Therefore, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention, and thus rendering the claim indefinite.

New Ground of Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a

person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 55, 85, 91, 117, 119 and 124 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alemany et al. (U. S. Patent No. 5,798,348) in view of Allison et al. (U. S. Patent Application Publication No. 2006/0083778), and further in view of Zhu et al. (Carcinogenesis, 1998, 19, page 1-27).

Applicant Claims

Applicant claims a method of lowering body weight in a mammal comprises administering an effective amount of substantially pure fatty acid monoester, or a precursor thereof, of an estrogen and a fatty acid in combination with an amount of at least one pharmaceutically acceptable excipients or cosmetically acceptable excipients; wherein the estrogen is a 2-hydroxy derivative of estrone, diethylstilbestrol, estriol, estradiol or ethinyl estradiol, and the fatty acid consists of more at least 20 carbon atoms,

with the proviso that the estrogen is steroidal and has a hydroxyl group at the C-3 position, where the fatty acid is conjugated with the steroid ring system through an acyl bond.

Determination of the scope and content of the prior art (MPEP 2141.01)

Alemany et al. teach a method for lowering the body weight in a mammal comprising the step of administering to said mammal an effective amount of a substantially pure fatty acid monoester of an estrogen and a fatty acid (column 1, line 6-8; column 2, line 16-18; column 3, line 34-36; and column 8, claim 15), wherein the estrogen is estrone, diethylstilbestrol, estriol, estradiol or ethinyl estradiol (column 1, line 57-59 and column 8, claims 1, 6 and 7) and the fatty acid is oleic acid (a fatty acid with 18 carbon atoms) or arachidonic acid (a fatty acid with 20 carbon atoms) (column 1, line 60-63; column 2, line 7-9; column 7, claims 1, 6 and 7).

Alemany et al. also teach that the fatty acid moiety and the estrogen moiety of the estrogen fatty acid monoester is linked by an ester linkage, where the acyl group of the fatty acid is attached to the C-3 hydroxyl group of the estrogen (column 2, line 10-12; column 7, claims 1, 6-7 and 20 and column 8, claim 15).

Alemany et al. further teach that the estrogen fatty acid monoester is administered in combination with an amount of at least one member selected from the group consisting of pharmaceutically acceptable excipients and cosmetically acceptable excipients which amount is sufficient for the purposes thereof (column 8, claim 15).

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

However, Alemany et al. do not teach that the estrogen moiety of the estrogen fatty acid monoester contains a hydroxyl group at the C-2 position. However, the deficiency is cured by the teachings of Allison et al. and Zhu et al.

Allison et al. teach a treatment method comprising the step of administering a formulation to an individual containing an estradiol metabolite in liposomes (page 11, claim 35).

Allison et al. teach that estradiol is converted into different derivatives through metabolic processes in vivo to form estradiol metabolites, i.e. catecholestrogens (catechol contains two hydroxyl groups at C2 and C3 position of the phenyl ring). Allison et al. also teach that the catecholestrogen, i.e. 2-hydroxyestradiol, is formed by hydroxylation of estrogen via cytochrome P450 enzymes (page 1, paragraph 0003, lines 1-6).

Allison et al. teach that the estradiol metabolite of use can be 2-hydroxyestradiol, which has been reported to have effects on number of cellular processes. Allison et al. also teach that 2-hydroxyestradiol has been shown to affect cholesterol levels in ovariectomized rats, to inhibit adipose cell proliferation in culture and to decrease the effects of obesity and metabolic syndrome (page 1, paragraph 0004, lines 1-10).

Zhu et al. teach that 2-hydroxylation of estrone to 2-hydroxyestrone is a major metabolic pathway that occurs in the liver by cytochrome P450 hydroxylase.

Finding of prima facie obviousness Rational and Motivation

(MPEP 2142-2143)

It would have been obvious to a person of ordinary skilled in the art at the time the invention was made to combine the teachings of Alemany et al. and Allison et al. and Zhu et al. to utilize a 2-hydroxyestrogen, i.e. 2-hydroxyestrone or 2-hydroxyestradiol, of fatty acid monoester to lower the body weight of a mammal to arrive at the instant invention.

One of ordinary skill would have been motivated to do this because it has been taught in the art by Alemany et al. that administration of estrone fatty acid monoester can lower the body weight in a mammal and it is also taught in the arts that 2-hydroxlestradiol which is a metabolite of estradiol can decrease the effects of obesity and inhibits adipose cell proliferation; similarly, 2-hydroxyestrone is a metabolite of estrone forming from the same mechanism in vivo by P450 cytochrome enzymes. Furthermore, the art, namely Alemany et al., already establish the concept of linking a fatty acid, i.e. arachidonic acid (it is a fatty acid consists of 20 carbon atoms) to an estrogen at the C-3 position of the estrogen in methods of lowering body weight in a mammal. Therefore, the instant application links a fatty acid consists of at least 20 carbon atoms to a 2-

hydroxy estrogen, with the same method utility is obvious and would expect to behave the same manner for lowering body weight in a mammal.

Therefore, the Examiner can only conclude that it would be obvious to administer a fatty acid monoester of 2-hydroxy estrogen, i.e. 2-hydroxyestrone or 2-hydroxyestradiol in a method of lowering body weight in a mammal because 2-hydroxyestrone or 2-hydroxyestradiol are functional equivalent estrogenic metabolites formed from the same mechanism by cytochrome P450 enzymes, and thus can be used interchangeably. The pharmaceutically acceptable excipients or cosmetically acceptable excipients is a routine practice, as taught by Alemany et al. and Allison et al., which would be dependent on the formulation of intended use.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

No claims are allowed.

Contact Information

Any inquiry concerning this communication from the Examiner should direct to Helen Mei-Ping Chui whose telephone number is 571-272-9078. The examiner can normally be reached on Monday-Thursday (7:30 am – 5:00 pm). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where the application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either PRIVATE PAIR or PUBLIC PAIR. Status information for unpublished applications is available through PRIVATE PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the PRIVATE PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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